

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 501/00, 499/00	A1	(11) International Publication Number: WO 97/17352 (43) International Publication Date: 15 May 1997 (15.05.97)
(21) International Application Number: PCT/EP96/04880 (22) International Filing Date: 6 November 1996 (06.11.96) (30) Priority Data: 95202992.4 6 November 1995 (06.11.95) EP (34) Countries for which the regional or international application was filed: NL et al. 007,278 6 November 1995 (06.11.95) US (71) Applicant (for all designated States except US): GIST-BROCADES B.V. [NL/NL]; Wateringseweg 1, P.O. Box 1, NL-2600 MA Delft (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): DE VROOM, Eric [NL/NL]; De Mey van Streefkerkstraat 65, NL-2313 JM Leiden (NL). VAN DER DOES, Thomas [NL/NL]; Van der Haertstraat 47, NL-2613 ZA Delft (NL). (74) Agents: VISSER-LUIRINK, Gesina et al.; Gist-Brocades N.V., Patents and Trademarks Dept., Wateringseweg 1, P.O. Box 1, NL-2600 MA Delft (NL).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: DE-ESTERIFICATION PROCESS (57) Abstract An efficient process for de-esterification has been provided for by application of special tetrahalogenides. By applying this process a new compound, viz. cefesone, and especially the E-isomer thereof, has been prepared.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

DE-ESTERIFICATION PROCESS

Technical field

5

The present invention relates to an improved method for ester hydrolysis. In particular, the invention relates to the deprotection of carboxyl esters by reaction with acidic metal halogenides (Lewis acids).

10

Background and relevant literature

The protection and deprotection of carboxyl esters is an important part of many syntheses wherein carboxylate groups are involved. For instance, this protection and deprotection does often play a role in the synthesis of semi-synthetic cephalosporins (SSC's) and semi-synthetic penicillins (SSP's). SSC's are derivatized congeners of 7-aminocephalosporanic acid (7-ACA) or 7-aminodesacetoxycephalosporanic acid (7-ADCA) and salts and esters thereof; SSP's are derivatized congeners of 6-aminopenicillanic acid (6-APA).

In synthetic schemes leading to SSC's and SSP's a variety of protecting groups is often employed. An important feature in protecting group strategy usually is blocking and deblocking of the carboxyl function since said carboxyl functions can undergo decarboxylation if left unreacted (J. Amer. Chem. Soc. 1969, 91, 1401). Protection is achieved using esterification with an alcohol that can be removed under acidic or neutral conditions. Important industrial examples of 4-carboxyl protecting groups are allyl, benzhydryl, benzyl, tert-butyl, 4-methoxybenzyl, 4-nitrobenzyl and trichloroethyl. The known methods for removal of protecting groups are either expensive (trifluoroacetic acid), difficult to process because of complexation (zinc/acetic acid), or suffer from low yields (hydrogenolysis in case of benzhydryl and benzyl).

It is accordingly an object of the present invention to provide a new and improved process for converting carboxyl esters to the corresponding acid in high yield without the production of unwanted by-products.

5 It is also an object of the invention to provide new compounds by the application of this process, as for instance (6R,7R)-3-(2,4-dinitrostyryl)-7-phenylacetamido-ceph-3-em-4-carboxylic acid (cefesone), and the conversion in salts and esters thereof, and the E-isomers of the same. The chemical name
10 of the racemic mixture has recently been indicated in J. Clin. Micr. 1995, 1665, but a process to prepare the same has not been published up to now.

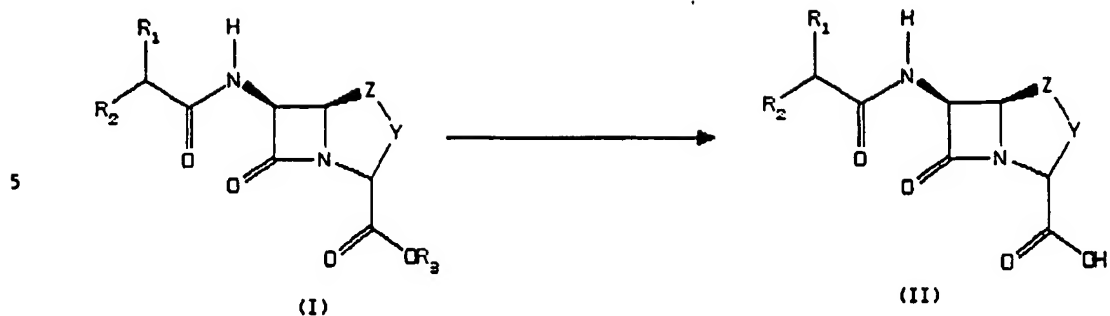
Aluminum trichloride-promoted hydrolysis of cephalosporin esters is a procedure reported for the hydrolysis of benzyl
15 esters (Tetrahedron Lett. 1979, 2793), benzhydryl esters (Pure & Appl. Chem. 1987, 59, 1041), and 4-methoxybenzyl esters (Pure & Appl. Chem. 1989, 61, 325).

Surprisingly, it has been found that other Lewis acids, like tellurium tetrachloride, tin tetrachloride or titanium
20 tetrachloride, can be applied for the high yield hydrolysis of carboxyl esters, such as tert-butyl and 4-methoxybenzyl.

Summary of the invention

25 The present invention provides a method for the hydrolysis of a carboxy-protected ester by reacting said ester with a compound selected from the group consisting of the tetrahalogenides of titanium, tin and tellurium.

Especially, the process of the present invention can be
30 applied advantageously for the hydrolysis of β -lactam esters of general formula (I) to give corresponding cephalosporin or penicillin derivatives of formula (II) as depicted in the scheme below. In particular, the esters are tert-butyl and 4-methoxybenzyl esters. The Lewis acid is selected from the group consisting of tellurium tetrahalogenide, tin tetrahalogenide and
35 titanium tetrahalogenide.



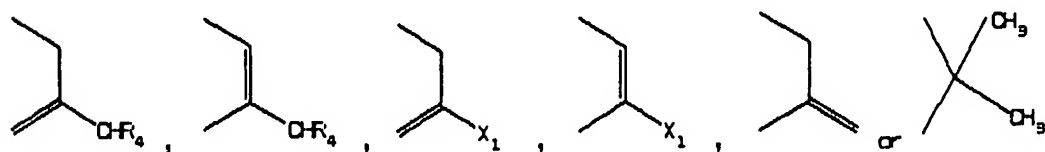
with R_1 is hydrogen, hydroxy, amine, halogen or lower alkyl;

10 R_2 is an optionally substituted phenyl or phenoxy or 5- or 6-membered heterocyclic ring;

R_3 is a carboxy-protecting group;

Z is oxygen, sulphur (optionally oxidized to sulfoxide or sulfone) or CHR_5 with R_5 is hydrogen or lower alkyl; and

15 Y is



with R_4 is optionally substituted alkylidene; and

X_1 is hydrogen, halogen or (lower) alkoxy or optionally substituted methyl or alkoxycarbonyl.

According to another aspect of this invention, the novel
25 compound (6R,7R)-3-(2,4-dinitrostyryl)-7-phenylacetamido-ceph-3-em-4-carboxylic acid and salts and esters thereof, especially the E-isomer, has been provided for.

Specific embodiments

30

According to the present invention, a process is provided for deesterification of carboxylate esters, for instance resulting in the preparation of 7-acylacetamido-cephem-4-carboxylic acids, 7-acylacetamido-cepham-4-carboxylic acids or 6-aminopenicillanic acid and pharmaceutically acceptable salts thereof
35 of formula (II), starting from the corresponding esters of formula (I). The deesterification usually will be carried out in

an organic solvent at a temperature of about -10°C - 20°C , preferably of about -5°C - 5°C .

The group R_1 can be optionally protected amino, halogen, hydrogen, optionally protected hydroxy or lower alkyl.

5 Preferably R_1 is hydrogen.

The acylamido group R_2 can be any group hitherto disclosed in the chemical literature and patent specifications or known to those skilled in the art of cephalosporin and penicillin chemistry. Preferably R_2 is one present in the 6β -side chain of
10 penicillins that can be obtained by fermentative procedures. The latter penicillins can be converted into cephalosporins by known methods. Suitable groups represented by R_2 are, for example, phenoxyacetamido, phenylacetamido and 2-thienylacetamido.

The group R_3 can be any group known to those skilled in the
15 art for protecting the carboxy group of cephalosporanic acid or penicillanic acid derivatives. Preferably R_3 represents an ester group which can be easily introduced. Particularly suitable ester groups are allyl, benzhydryl, benzyl, 2-bromoethyl, tert-butyl, 4-methoxybenzyl, methyl, 4-nitrobenzyl and 2,2,2-tri-
20 chloroethyl.

The group R_4 can be a C1-C6 alkylidene group like propenyl, optionally substituted by substituents like an acyl or heterocyclic group, optionally substituted by for instance halogen, hydroxy or nitro groups.

25 Examples of β -lactam derivatives that may be produced by the process of this invention are intermediates for antibiotics such as cefamandole, cefatrizine, cefdinir, cefixime, cefmenoxime, cefpodoxime, cefprozil, cefroxadine, ceftibuten, cef-
tiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, lora-
30 carbef, moxalactam, and also active compounds such as said antibiotics. Furthermore, using the process of this invention, β -lactamase indicating compounds such as cefesone and nitrocefin can be prepared.

The starting materials used in the present invention are
35 prepared according to methods published earlier. 3-Alkenyl substituted cephem derivatives can be prepared as described in European patent applications 292,806 and 421,219, and German

patent 2,249,165. 3-Acetoxymethyl-, 3-methyl- and 3-thiomethyl substituted cephem derivatives are prepared according to Recl. Trav. Chim. Pays-Bas 1993, 112, 66. 3-Methylene cepham derivatives are prepared according to United States patent 4,985,554.

- 5 Tert-butyl-(6R,7R)-3-(2,4-dinitrostyryl)-7-phenylacetamido-ceph-3-em-4-carboxylate can be prepared by reacting the corresponding (2-halo)-3-halomethyl-3-cephem compound, viz. tert-butyl-(1S,6R,7R)-(2-halo)-3-halomethyl-1-oxo-7-phenylacetamido-3-cephem-4-carboxylate, with a phosphine according to EP-B-0299587
10 followed by reduction using phosphorous trichloride and condensation with 2,4-dinitrobenzaldehyde.

Methods of analysis

- 15 HPLC Column: Chrompack Microsphere C18, 3 μ m (100 x 3.0 mm).
Solvent: 30% Acetonitrile and 1% tetrahydrofuran in 7 mM potassium dihydrogenphosphate, pH 2.6.
Flow: 1.2 ml.min⁻¹.
Detection: 254 nm.
- 20 Retention: 7-phenylacetamido-3-deacetoxycephaloporanic acid (3.70 min); (6R,7R)-7-phenylacetamido-3-[(E)-1-propenyl]-ceph-3-em-4-carboxylic acid (8.02 min); (6R,7R)-7-phenylacetamido-3-[(Z)-1-propenyl]-ceph-3-em-4-carboxylic acid (6.20 min).
- 25 IR Infrared spectra were recorded on a Pye Unicam PU9714.
- MS Mass spectra were obtained with an AMD 402 mass spectrometer.
- NMR ¹H NMR spectra were recorded on a Bruker AM 360 MHz instrument. Purities were determined with ¹H NMR spectroscopy
30 using an internal reference.
- TLC Thin layer chromatography was performed using Merck Kiesel-gel 60 F₂₅₄ plates as stationary phase and ethylacetate/toluene/acetic acid 4/3/2/1 as mobile phase.

Example 1**Synthesis of (6R,7R)-3-methyl-7-phenylacetamido-ceph-3-em-4-carboxylic acid**

5 A stirred solution of tert-butyl (6R,7R)-3-methyl-7-phenylacetamido-ceph-3-em-4-carboxylate (0.873 g, purity 89%, 2.0 mmol) in dichloromethane (50 ml) was cooled to -20°C. Titanium tetrachloride (0.88 ml, 7.9 mmol) was added in 1 min. After stirring for 2 h at 0°C, the suspension was mixed with a chilled
10 2 M solution of hydrochloric acid in water (40 ml). The organic phase was separated and water was added. The pH was adjusted to 7.0 with a 2 M solution of sodium hydroxide in water and the aqueous phase was separated and the pH was adjusted to 2.0 with a 2M solution of hydrochloric acid in water. A white product
15 precipitated which was isolated and dried to give 0.49 g of (6R,7R)-3-methyl-7-phenylacetamido-ceph-3-em-4-carboxylic acid (purity 94%, yield 69.4%).

IR (KBr): 3270 cm⁻¹, 1770 cm⁻¹, 1700 cm⁻¹, 1655 cm⁻¹, 1550 cm⁻¹.

¹H NMR (DMSO-d₆; 360 MHz): δ = 2.03 (s, 3 H), 3.35/3.54 (ABq, 2 H, J = 16.7 Hz), 3.55/3.62 (ABq, 2 H), 5.05 (d, 1 H, J = 5.0 Hz), 5.60 (dd, 1 H), 7.3 (m, 5 H), 9.07 (d, 1 H, J = 6.9 Hz)
20 ppm.

Example 2**25 Synthesis of (4R,6R,7R)-3-methylene-7-phenylacetamido-cepham-4-carboxylic acid**

A stirred solution of tert-butyl (4R,6R,7R)-3-methylene-7-phenylacetamido-cepham-4-carboxylate (0.83 g, purity 93.7%,
30 2.0 mmol) in dichloromethane (80 ml) was cooled to 0°C. Titanium tetrachloride (0.66 ml, 6.0 mmol) was added in 1 min. After stirring for 4 h at 0°C, the suspension was mixed with a chilled 2 M solution of hydrochloric acid in water (40 ml). The organic phase was separated and washed with a 1 M solution of hydrochloric acid in water (20 ml), water (20 ml), and brine (20 ml).
35 The organic phase was dried over magnesium sulphate and evapor-

ated to give 0.40 g of (4R,6R,7R)-3-methylene-7-phenylacetamido-cepham-4-carboxylic acid (purity 75%, yield 45.1%).

IR (KBr): 3280 cm^{-1} , 1745 cm^{-1} , 1635 cm^{-1} .

^1H NMR (CDCl_3 ; 360 MHz): δ = 3.17 (d, 1 H, J = 15.0 Hz), 3.56/
5 3.68 (m, 3 H), 5.07 (s, 1 H), 5.23 (ABq, 2H, J = 12.5 Hz), 5.64
(dd, 1 H), 6.29 (d, 1H, J = 11.0 Hz), 7.3 (m, 5 H).

Example 3

Synthesis of (4R,6R,7R)-3-methyl-7-phenylacetamido-ceph-2-em-4-
10 carboxylic acid

A stirred solution of tert-butyl (4R,6R,7R)-3-methyl-7-phenylacetamido-ceph-2-em-4-carboxylate (0.776 g, 2.0 mmol) in dichloromethane (30 ml) was cooled to 0°C. Titanium tetra-
15 chloride (0.6 ml, 5.5 mmol) was added in 1 min. After stirring for 2.5 h at 0°C, the suspension was mixed with a chilled 2 M solution of hydrochloric acid in water (40 ml). The organic phase was separated and washed with a 1 M solution of hydrochloric acid in water (20 ml), water (20 ml), and brine (20 ml).
20 The organic phase was concentrated to give 0.55 g of (4R,6R,7R)-3-methyl-7-phenylacetamido-ceph-2-em-4-carboxylic acid (yield 82.7%).

Example 4

25 Synthesis of (6R,7R)-3-methyl-7-phenoxyacetamido-ceph-3-em-4-carboxylic acid

A stirred solution of tert-butyl (6R,7R)-3-methyl-7-phenoxyacetamido-ceph-3-em-4-carboxylate (0.41 g, 1.0 mmol) in
30 dichloromethane (25 ml) was cooled to 0°C. Titanium tetrachloride (0.38 ml, 3.5 mmol) was added in 1 min. A yellow precipitate was formed which was stirred for 2 h at 0°C. To the suspension was added a chilled 1 M solution of hydrochloric acid in water (40 ml). The organic phase was separated, washed with
35 water and brine, dried over magnesium sulphate, and evaporated to give 0.30 g of (6R,7R)-3-methyl-7-phenoxyacetamidoceph-3-em-4-carboxylic acid (purity 63%, yield 54.3%).

IR (KBr): 3375 cm^{-1} , 1755 cm^{-1} , 1740 cm^{-1} , 1655 cm^{-1} .

^1H NMR ($\text{DMSO}-d_6$; 360 MHz): δ = 2.06 (s, 3 H), 3.42/3.47 (ABq, 2 H, J = 8.3 Hz), 3.59/3.64 (ABq, 2 H, J = 16.6 Hz), 5.08 (d, 1 H), 5.66 (dd, 1 H), 6.3 (m, 5 H), 9.02 (d, 1 H, J = 9.9 Hz)
5 ppm.

Example 5

Synthesis of (6R,7R)-7-phenylacetamido-3-(1-propenyl)-ceph-3-em-4-carboxylic acid, Z-isomer

10

A stirred solution of 4-methoxybenzyl (6R,7R)-7-phenylacetamido-3-(1-propenyl)-ceph-3-em-4-carboxylate (0.509 g, purity 9% E-isomer, 84% Z-isomer, 0.99 mmol) in dichloromethane (15 ml) was cooled to 2°C. Titanium tetrachloride (0.5 ml, 4.5 mmol) was
15 added in 1 min. After 30 min the brown suspension was mixed with a chilled mixture of dichloromethane (50 ml) and a 2 M solution of hydrochloric acid in water (50 ml). The organic phase was separated and extracted with a 2 M solution of hydrochloric acid in water (3 x 50 ml). The aqueous phases were extracted with
20 dichloromethane (25 ml). The combined organic phases were analyzed using HPLC: 0.036 g (6R,7R)-7-phenylacetamido-3-[(E)-1-propenyl]-ceph-3-em-4-carboxylic acid (0.10 mmol, yield 10.2%); 0.301 g (6R,7R)-7-phenylacetamido-3-[(Z)-1-propenyl]-ceph-3-em-4-carboxylic acid (0.84 mmol, yield 84.8%). The overall yield
25 is therefore 95.0%.

Example 6

Screening of lewis acids in the hydrolysis of tert-butyl (6R,7R)-7-phenyl-acetamido-3-(1-propenyl)-ceph-3-em-4-carboxylate
30

To a stirred solution of tert-butyl (6R,7R)-7-phenylacetamido-3-(1-propenyl)-ceph-3-em-4-carboxylate in dichloromethane (30 ml.g^{-1}) was added Lewis acid (3-5 equiv., see table for
35 conditions). The formation of (6R,7R)-7-phenylacetamido-3-(1-propenyl)-ceph-3-em-4-carboxylic acid was monitored either by HPLC or TLC. The results are summarized in the table.

	Lewis acid	T (°C)	Time (h)	Yield (%)	Remarks
	AlCl ₃	25	28	50	According to TLC; some degradation observed.
5	BCl ₃	-10	4	20	According to TLC; extensive degradation observed.
	BF ₃	25	18	0	According to TLC; no product, no starting material.
10	FeCl ₃	5	2.5	34	According to HPLC; yield after work-up.
	SiCl ₄	25	72	0	According to TLC; no reaction observed.
	SnCl ₄	-10	2.5	88	According to HPLC; tin-residues are difficult to remove during work-up.
15	TiCl ₄	5	3	91	According to HPLC.

Example 7

Synthesis of (1S,6R,7R)-3-acetoxymethyl-1-oxo-7-phenylacetamido-ceph-3-em-4-carboxylic acid

To a stirred solution of tert-butyl (1S,6R,7R)-3-acetoxymethyl-1-oxo-7-phenylacetamido-ceph-3-em-4-carboxylate (0.23 g, purity 89.3%, 0.423 mmol) in acetonitrile (2.5 ml) was added a solution of tellurium tetrachloride (0.135 g, 0.5 mmol) in acetonitrile (2.5 ml). After stirring for 1 h at 23°C, the crystalline precipitate was collected by filtration, washed with acetonitrile (0.5 ml) and dried over phosphorous pentachloride under vacuum to give 0.147 g of (1S,6R,7R)-3-acetoxymethyl-1-oxo-7-phenylacetamido-ceph-3-em-4-carboxylic acid (purity 87%, 75.1% yield). The filtrate was treated with ether (10 ml) to give a second crop of product (0.008 g, purity 82%, 3.9% yield). The total yield is 79.0%.

Example 8**Synthesis of (6R,7R)-7-phenylacetamido-3-(1-propenyl)-ceph-3-em-4-carboxylic acid, Z-isomer**

5 At 0°C, titanium tetrachloride (420 ml, 3.82 mol) was added in 30 min to a solution of tert-butyl (6R,7R)-7-phenylacetamido-3-(1-propenyl)-ceph-3-em-4-carboxylate, (404.8 g, 976.5 mmol; ratio E-isomer : Z-isomer = 0.05). After stirring for 1 h at 1±1°C, the solution is transferred to a stirred 2 M solution of
10 hydrochloric acid in water (6.00 l). The layers are separated and the aqueous phase was back-extracted with dichloromethane (800 ml). The combined organic phases were extracted with a 2 M solution of hydrochloric acid in water (3 x 3l) and each batch of water was back-extracted with the wash-dichloromethane. The
15 combined organic phases (6.03 l) were analyzed using HPLC: 16.9 g (6R,7R)-7-phenylacetamido-3-[(E)-1-propenyl]-ceph-3-em-4-carboxylic acid (47.2 mmol, yield 4.8%); 296.1 g (6R,7R)-7-phenylacetamido-3-[(Z)-1-propenyl]-ceph-3-em-4-carboxylic acid (826.1 mmol, yield 84.6%). The overall yield is therefore 89.4%.

20

Example 9**Synthesis of (6R,7R)-3-(2,4-dinitrostyryl)-7-phenylacetamido-ceph-3-em-4-carboxylic acid, E-isomer**

25 A stirred solution of tert-butyl (6R,7R)-3-(2,4-dinitrostyryl)-7-phenylacetamido-ceph-3-em-4-carboxylate (67.41 g, purity 8% E-isomer, 81% Z-isomer, 105.9 mmol) in dichloromethane (1685 ml) was cooled to -25°C. Titanium tetrachloride (53 ml, 482 mmol) was added in 10 min and the temperature was
30 brought to 0°C. After 105 min a chilled 2 M solution of hydrochloric acid in water was added at such a rate that the temperature remained under 10°C. The organic phase was separated and extracted with a 2 M solution of hydrochloric acid in water (2 x 1685 ml) and brine (1685 ml). The organic phase was concen-
35 trated under reduced pressure to give an orange foam. Crude product thus obtained was crystallized by dissolving in acetone (1350 ml) at 65°C and adding water (675 ml). Crystallization

was allowed to proceed for 16 h at 0°C and the crystals were collected by filtration. Recrystallization of the product was performed by dissolving the material in acetone/acetic acid (2:1) at 53°C, removing solvent (1700 ml) by evaporation under reduced pressure and stirring for 16 h at 20°C. Crystals were collected by filtration, washed with acetic acid (300 ml) and ether (250 ml), and dried under vacuum at 45°C to give 34.33 g (purity 99% E-isomer, 66.6 mmol; yield 63%) of (6R,7R)-3-(2,4-dinitrostyryl)-7-phenylacetamido-ceph-3-em-4-carboxylic acid as yellow crystals.

IR (KBr): 3300 cm⁻¹, 1780 cm⁻¹, 1715 cm⁻¹, 1625 cm⁻¹, 1525 cm⁻¹.

MS (DCI): m/z = 528.0 (MNH₄⁺).

¹H NMR (CDCl₃/DMSO-d₆, 1:2; 360 MHz): δ = 3.50/3.58 (ABq, 2 H, J = 14.1 Hz), 3.62/3.77 (ABq, 2 H, J = 17.5 Hz), 5.05 (d, 1 H, J = 4.9 Hz), 5.72 (dd, 1 H, J_{6,7} = 4.9 Hz, J_{7,NH} = 8.3 Hz), 7.3 (m, 6 H), 7.63 (d, 1 H, J = 16.1 Hz), 7.82 (d, 1 H, J = 8.8 Hz), 8.33 (dd, 1 H, J₁ = 2.1 Hz, J₂ = 8.8 Hz), 8.66 (d, 1 H, J = 2.1 Hz), 8.97 (d, 1 H, J = 8.3 Hz) ppm.

Example 10

Synthesis of (6R,7R)-7-phenylacetamido-3-(1-phenyl-1-H-tetrazol-5-yl)thiomethyl-ceph-3-em-4-carboxylic acid

A stirred solution of tert-butyl (6R,7R)-7-phenylacetamido-3-(1-phenyl-1-H-tetrazol-5-yl)thiomethyl-ceph-3-em-4-carboxylate (1.0 g, purity 80%, 1.42 mmol) in dichloromethane (50 ml) was cooled to 0°C. Titanium tetrachloride (0.62 ml, 5.6 mmol) was added in 1 min. After stirring for 1 h at 0°C, the suspension was mixed with a chilled 2 M solution of hydrochloric acid in water (40 ml). The organic phase was separated and washed with a 1 M solution of hydrochloric acid in water (20 ml), water (20 ml), and brine (20 ml). The organic phase was dried over magnesium sulphate and evaporated to give 0.55 g of (6R,7R)-7-phenylacetamido-3-(1-phenyl-1-H-tetrazol-5-yl)thiomethyl-ceph-3-em-4-carboxylic acid (purity 60%, yield 45.8%).

IR (KBr): 3260 cm⁻¹, 1770 cm⁻¹, 1485 cm⁻¹.

¹H NMR (DMSO-d₆; 360 MHz): δ = 1.25 (s, 2H), 3.47/3.65 (m, 2 H), 3.68 (ABq, 2H, J = 11.7 Hz), 4.28 (d, 1H, J = 13.3 Hz), 4.56 (d, 1H, J = 13.3 Hz), 5.04 (d, 2H, J = 6.1 Hz), 5.71 (m, 2H), 7.01 (m, 1H), 7.2/7.8 (m, 10 H), 9.14 (d, 1H, J = 11.5 Hz).

5

Example 11

Synthesis of (6R,7R)-7-phenylacetamido-3-(1-phenyl-1-H-tetrazol-5-yl)thiomethyl-ceph-3-em-4-carboxylic acid

10 A stirred solution of tert-butyl (6R,7R)-7-phenylacetamido-3-(1-phenyl-1-H-tetrazol-5-yl)thiomethyl-ceph-3-em-4-carboxylate (1.0 g, purity 80%, 1.42 mmol) in dichloromethane (50 ml) and anisole (0.93 ml) was cooled to 0°C. Titanium tetrachloride (0.62 ml, 5.6 mmol) was added in 1 min. After stirring for 2.5 h
15 at 0°C, the suspension was mixed with a chilled 2 M solution of hydrochloric acid in water (40 ml). The organic phase was separated and washed with a 1 M solution of hydrochloric acid in water (20 ml), water (20 ml), and brine (20 ml). The organic phase was dried over magnesium sulphate and evaporated to give
20 0.60 g of (6R,7R)-7-phenylacetamido-3-(1-phenyl-1-H-tetrazol-5-yl)thiomethyl-ceph-3-em-4-carboxylic acid (purity 60%, yield 49.9%).

IR (KBr): 3260 cm⁻¹, 1770 cm⁻¹, 1485 cm⁻¹.

¹H NMR (DMSO-d₆; 360 MHz): δ = 1.25 (s, 2H), 3.47/3.65 (m, 2 H),
25 3.68 (ABq, 2H, J = 11.7 Hz), 4.28 (d, 1H, J = 13.3 Hz), 4.56 (d, 1H, J = 13.3 Hz), 5.04 (d, 2H, J = 6.1 Hz), 5.71 (m, 2H), 7.01 (m, 1H), 7.2/7.8 (m, 10 H), 9.14 (d, 1H, J = 11.5 Hz).

Example 12

30 Synthesis of (6R,7R)-7-phenylacetamido-3-(1-phenyl-1-H-tetrazol-5-yl)thiomethyl-ceph-3-em-4-carboxylic acid

A stirred solution of tert-butyl (6R,7R)-7-phenylacetamido-3-(1-phenyl-1-H-tetrazol-5-yl)thiomethyl-ceph-3-em-4-carboxylate
35 (5.0 g, purity 80%, 7.09 mmol) in dichloromethane (150 ml) was cooled to 0°C. A solution of titanium tetrachloride (2.33 ml, 21.2 mmol) in dichloromethane (15 ml) was added. After stirring

for 4.5 h at 0°C, the suspension was mixed with a chilled 2 M solution of hydrochloric acid in water. The organic phase was separated and washed with a 1 M solution of hydrochloric acid in water, water, and brine. The organic phase was dried over magnesium sulphate and concentrated to give 3.55 g of (6R,7R)-7-phenylacetamido-3-(1-phenyl-1-H-tetrazol-5-yl)thiomethyl-ceph-3-em-4-carboxylic acid (purity 60%, yield 59.1%).

IR (KBr): 3260 cm⁻¹, 1770 cm⁻¹, 1485 cm⁻¹.

¹H NMR (DMSO-d₆; 360 MHz): δ = 1.25 (s, 2H), 3.47/3.65 (m, 2H), 3.68 (ABq, 2H, J = 11.7 Hz), 4.28 (d, 1H, J = 13.3 Hz), 4.56 (d, 1H, J = 13.3 Hz), 5.04 (d, 2H, J = 6.1 Hz), 5.71 (m, 2H), 7.01 (m, 1H), 7.2/7.8 (m, 10 H), 9.14 (d, 1H, J = 11.5 Hz).

Example 13

15 Synthesis of (6R,7R)-7-phenylacetamido-3-(pyrimidin-2-yl)thiomethyl-ceph-3-em-4-carboxylic acid

A stirred solution of tert-butyl (6R,7R)-7-phenylacetamido-3-(pyrimidin-2-yl)thiomethyl-ceph-3-em-4-carboxylate (3.5 g, 20 purity 53%, 3.71 mmol) in dichloromethane (150 ml) and anisole (4.65 ml) was cooled to 0°C. A solution of titanium tetrachloride (2.3 ml, 21 mmol) in dichloromethane (10 ml) was added. After stirring for 3.5 h at 0°C, the suspension was mixed with a chilled 2 M solution of hydrochloric acid in water. The organic phase was separated and washed with a 1 M solution of hydrochloric acid in water, water, and brine. The organic phase was dried over magnesium sulphate and concentrated to give 2.10 g of (6R,7R)-7-phenylacetamido-3-(pyrimidin-2-yl)thiomethyl-ceph-3-em-4-carboxylic acid (purity 75%, yield 50.9%).

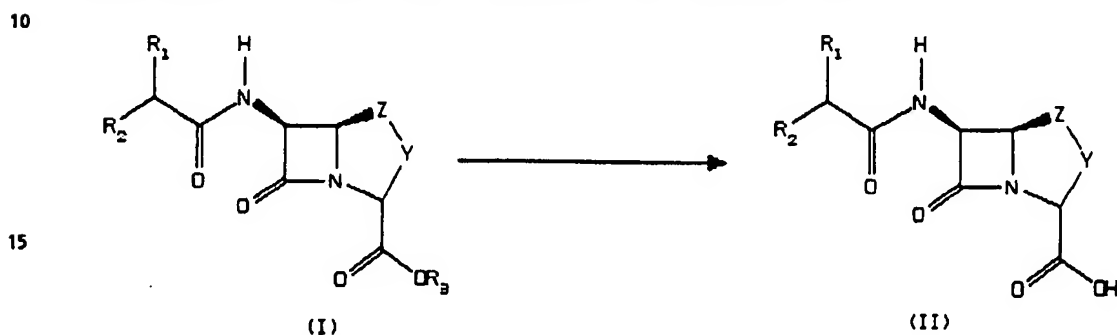
30 IR (KBr): 3240 cm⁻¹, 1760 cm⁻¹, 1695 cm⁻¹, 1640 cm⁻¹, 1525 cm⁻¹.

¹H NMR (DMSO-d₆; 360 MHz): δ = 2.52 (s, 1H), 3.47/3.64 (ABq, 2 H, J = 12.5 Hz), 3.75/4.02 (m, 2H), 4.60 (d, 1H, J = 15.0 Hz), 5.08 (d, 1H, J = 5.0 Hz), 5.62 (ABq, 1H, J = 5.0 Hz), 7.28 (m, 6H), 8.68 (d, 2H, J = 3.4 Hz), 9.15 (d, 1H, J = 10.0 Hz).

Claims

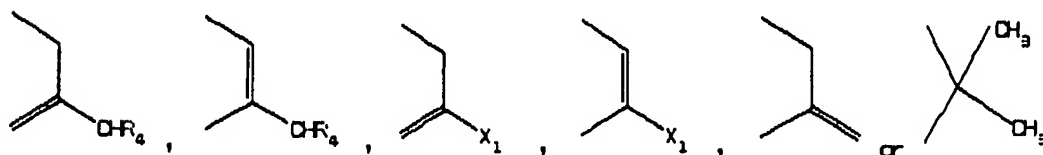
1. Process for the hydrolysis of an ester, characterized by reacting said ester with a compound selected from the group consisting of the tetrahalogenides of titanium, tin and tellurium.

2. A process according to claim 1, characterized by the hydrolysis of a β -lactam ester of formula (I)



with R_1 is hydrogen, hydroxy, amine, halogen or lower alkyl;
 R_2 is an optionally substituted phenyl or phenoxy or 5- or
 20 6-membered heterocyclic ring;
 R_3 is a protecting group;
 Z is oxygen, sulphur (optionally oxidized to sulfoxide or
 sulfone) or CHR_5 with R_5 is hydrogen or lower alkyl; and
 Y is

25



30

with R_4 is optionally substituted alkylidene; and
 X_1 is hydrogen, halogen or (lower) alkoxy or optional-
 ly substituted methyl or alkoxycarbonyl.

35 3. A process according to claim 1, characterized by the hydrolysis of a tert-butyl or 4-methoxybenzyl ester.

4. A process according to any one of the claims 1-3, characterized by the application of a compound selected from the group titanium tetrachloride, tin tetrachloride and tellurium tetrachloride.

5

5. (6R,7R)-3-(2,4-dinitrostyryl)-7-phenylacetamido-ceph-3-em-4-carboxylic acid and salts and esters thereof.

6. The E-isomer of (6R,7R)-3-(2,4-dinitrostyryl)-7-phenyl-
10 acetamido-ceph-3-em-4-carboxylic acid and of salts and esters thereof.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/EP 96/04880

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D501/00 C07D499/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 132 987 (ELI LILLY AND COMPANY) 13 February 1985 *Document* *Page 2: line26-27* ---	1-4
X	FR,A,2 342 974 (SHIONOGI & CO) 30 September 1977 *Page 16: claim 4* *Document* ---	1-4
X	DE,A,27 25 519 (SHIONOGI & CO) 21 December 1978 *Document* *Page 2 : claim 5* --- <div style="text-align: right;">-/--</div>	1-4
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*a* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center;">11 February 1997</div>		Date of mailing of the international search report <div style="text-align: center;">20.02.97</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016		Authorized officer <div style="text-align: center;">Luyten, H</div>

INTERNATIONAL SEARCH REPORT

Int. .onal Application No
PCT/EP 96/04880

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>JOURNAL OF CLINICAL MICROBIOLOGY, vol. 33, no. 6, June 1995, pages 1665-1667, XP002024966 GARY V. DOERN ET AL: cited in the application *Page 1665: column 1;last paragraph* -----</p>	5,6

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/EP 96/04880

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0132987	13-02-85	CA-A- 1218646 GB-A,B 2143529 JP-A- 60048936	03-03-87 13-02-85 16-03-85
FR-A-2342974	30-09-77	JP-A- 52106891 BE-A- 852054 CA-A- 1069886 CH-A- 630333 DE-A- 2709292 GB-A- 1569040 NL-A,B,C 7702242 SE-B- 443563 SE-A- 7702307 US-A- 4223132	07-09-77 05-09-77 15-01-80 15-06-82 08-09-77 11-06-80 06-09-77 03-03-86 04-09-77 16-09-80
DE-A-2725519	21-12-78	NONE	